REMARKS

According to the official action, claims 14 and 15 are anticipated by WO97/09877 (Aggarwal). This is respectfully traversed.

Aggarwal teaches that curcumin inhibits activation of NF-kB. Aggarwal states that curcumin may be given in any dose which suitably inhibits the activation of the NF-kB transcription factor.

Aggarwal also states that the present invention is also directed to a method of inhibiting the nuclear translocation of the p65 subunit of the NF-kB transcription factor in a cell in an animal in need of such treatment. Aggarwal states the preferably the human has a pathophysiological state selected from the group consisting of toxic/septic shock, graft vs. host reaction, radiation damage, atherosclerosis, AIDs, inflammation and cancer. There is no in vivo data in Aggarwal and there is nothing to support that administration of curcumin has any affect on any of these conditions. Aggarwal states that a method of inhibiting the phosphorylation and degradation of IkB protein in a cell or in an animal is relevant where the human has a pathophysiological state selected from the group consisting of toxic/septic shock, graft vs. host reaction, radiation damage, atheroscloerosis and cancer. Aggarwal does not provide any evidence that curcumin has any effect on these conditions. In fact, on page 13 of the specification, Aggarwal speculates that intervention in NF-kB activation may be beneficial in suppressing toxic/septic shock, graft-vs-host reactions, acute inflammatory reactions, HIV replication, acute phase response and radiation damage.

Aggarwal is replete with speculative statements. As stated above Aggarwal

speculates that intervention in NF-kB activation may be beneficial in suppressing toxic/septic shock, graft-vs-host reactions, acute inflammatory reactions, HIV replication, acute phase response and radiation damage. However, Aggarwal provides no evidence that intervention in NF-kB activation may be beneficial in suppressing toxic/septic shock, graft-vs-host reactions, acute inflammatory reactions, HIV replication, acute phase response and radiation damage and no evidence that curcumin activates NF-kb and that curcumin has any effect in vivo where numerous other systems are in play.

In fact in example 7, it is shown that Curcumin by itself did not activate NF-B. TNF response was inhibited only when cells were pretreated with curcumin. In the description of example 9, it is shown that curcumin had no effect on the Sp1 transcription factor and that the DNA binding of AP-1 transcription factors was found to be down-modulated.

This is different than the subject matter of claims 14 and 15. This teaches that TNF response was only inhibited when the cells were pretreated with curcumin. Claim 14 defines administration of curcumin after septic shock.

On page 13 it is stated that "Identifying how curcumin blocks the activation of NF-B requires an understanding of the mechanism by which various induceers activate this important transcription factors. There is no discussion that any of the factors function in their "normal" manner when the animal has septic shock.

Aggarwal states that curcumin due to its ability to modulate activation of NF- B by various agents, curcumin has a high potential for use in modulating

expression of genes regulated by NF- B. Aggarwal has not established that modulation of NF-B has any role in treatment of septic shock.

In the application in issue, it is demonstrated by in vivo experiments that curcumin inhibits neutrophil infiltration in mice and this prevents or protects from septic shock conditions.

Neutrophil infiltration can be inhibited without involving NF-kB. It has been shown that other pathways without involving NF-kB could be blocked for inhibiting neutrophils. There are conditions where neutrophil infiltration may continue even if one inhibits NF-kB as explained previously. In fact, neutrophil infiltration may be inhibited by curcumin only in a patient with septic shock.

In example 10, it is described that reducing agents do not reverse the effect of curcumin.

Example 11 describes that curcumin inhibits TNF-dependent phosphorylation and degradation of Iba and translocation of p65 subunit of NF- B.

Aggarwal (WO 9709877) teaches that curcumin inhibits TNF-α induced activation of NF-β. It may be noted that TNF-α is only one of the mediators of septic shock. In the endotoxin shock model used by us, LPS is being administered to the animals to induce symptoms of septic shock. Septic shock is a pathological condition resulting from complex interactions of various mediators like cell adhesion molecules viz., ICAM-1, VCAM-1 and E-selection, P-selectin, L-selectin, proinflammatory cytokines and chemokines, like IL-1, TNF-a, nitric oxide, MIP-1a,

CINC, CCR5, CSCR3 etc. whose expressions, in turn, may be up-regulated or down-regulated in septic shock condition based on the intricate up or down regulation of various biochemical pathways and physiological mechanisms occuring at the *in vivo* level.

It may be noted that Aggarwal claims that prevention of TNFα-induced effect is protective for treating septic shock and that too without any experimental evidence. On the contrary, Meisner et al shown protective effect of PDTC *in vivo* even with elevated levels of TNFα-. Therefore Aggarwal does not anticipate the use of curcumin as an anti-septic agent. Further, there are reports which very clearly indicate that septic shock or inflammation could be NF-kB-independent (Joshi-Barve et al, 2003; Faouzi et al. 2001).

Therefore, it is not justified to predict/or assume any agent for its therapeutic value just on the basis of *in vitro* experiments as enough contradictions and opposite effects have been observed in *in vivo* experiments (a few examples (1-3) are mentioned below). The reason behind this is clear. *In vitro* experiments of evaluating any compound show its effect on only one or few parameters. In the body thousands and more biological reactions are going on. An agent which affects only one of a few parameters *in vitro* may affect many other additional parameters also in the body which may or may not be favorable to alleviate the targeted disease. The agent will be anti-disease only when it really alleviates that particular targeted disease in the intact body.

It has been mentioned in scientific publications that flavonoids have

beneficial effects including anti-aging properties (Kim et al, 2004; Middleton et al, 2000) but many of them have potential toxic effects (Galati and O'Brien, 2004). For example, quercetin being a flavonoid and an anti-oxidant (Lee et al, 1982; Lanni and Becker, 1985; Kim et al, 2004) should have anti-aging property. However, when experiments were done in animal models, it showed just opposite effect, that is, it reduced the life span of mice (Jones and Hughes, 1982).

Asthma is a very well known inflammatory disease but only a few anti-inflammatory drugs are used for therapeutic purpose, such as steroids. Other very popular anti-inflammatory drugs such as aspirin and several other aspirin-like compounds, COXIB etc. do not work. On the contrary, these drugs aggravate asthma (Sanchez-Borges et al, 2004; Simon, 2004).

Similarly, Clemastine, Kitotifen and Azelastine, which are very strong histamine release inhibitors, and supposed to have anti-asthmatic effect. However, when these were tested *in vivo*, showed no significant effect on asthmatic features, such as airway hyperresponsiveness (Nogrady and Bevan, 1978; Albazzaz and Patel 1988, Cockroft 1992).

Further, it should be noted that many dietary ingredients may be non-toxic and essential for food, which may be predicted for any therapeutic activity. This does not mean that all food constituents would be therapeutic, unitl they are tested for a particular disease. Similarly, while curcumin is undoubtedly a non-toxic and a very good anti-inflammatory compound, only the experimental demonstration or scientific proof, will disclose the therapeutic activity of it.

It is has not established by Aggarwal that curcumin can treat septic shock. Therefore, it is disclosed and it not inherent that curcumin has any effect on septic shock.

Therefore, it is respectfully requested that the rejection be withdrawn.

According to the action, Claims 9-12 and 16 are rejected as being obvious over Aggarwal in view of Ammon (US patent 5,401,777). This is respectfully traversed.

As explained above, Aggarwal does not disclose the claimed invention. Aggarwal and Ammon either alone or in combination suggest the claimed invention. There is no disclosure or suggestion in Aggarwal or Ammon that curcumin can be administered to treat toxic shock symptoms, that it has an affect on neutrophils and that it can be administered in an amount that is effective to prevent neutrophil infiltration from blood vessels to underlying tissues.

It is noted that Ammon, discloses that curcumin in vitro activity of a key enzyme in the biosynthesis of leucotrienes (citing to a 1985) published reference and that claim 1 of the patent is "A method for treatment of a patient susceptible to a condition associated with pathophysiological formation of leucotrienes, the method comprising: administering to said patient a pharmacologically effective amount of a preparation comprising curcumin or a curcumin derivative to reduce said formation of said leucotrienes.

The standard test used to establish prima facie obviousness is the test set

out by the Supreme Court in Graham v. John Deere (383 US 1, 148 USPQ 459 (1966)). To determine whether a claim is prima facie obvious:

1) the scope and content of the prior art are to be determined;
2) the differences between the prior art and the claims at issue are to be ascertained; and
3) the level of ordinary skill in the pertinent art resolved.

In addition, according to MPEP 2141, citing Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n. 5 (Fed. Cir. 1986), when applying 35 USC 103, the following tenets of patent law must be adhered to:

1) the claimed invention must be considered as a whole;
2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; and
3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention.

Reasonable expectation of success is the standard with which obviousness is determined. In re Merck & Co., Inc., 800 F.2d109, 231 USPQ 375 (Fed. Cir. 1986).

The reason, suggestion or motivation to combine references may be found explicitly or implicitly. While the references need not expressly teach that the disclosure contained therein should be combined with another, the showing of

combinability must be clear and particular. Ruiz v. A.B. Chance Co., 57 USPQ2d 1161 (Fed. Cir. 2000).

Considering the claimed invention as a whole, considering the references as a whole there is no suggestion of the claimed invention.

There is no disclosure or suggestion in the prior art of what the applicants have done so prima facie claims cannot be obvious.

It is respectfully requested that the rejection be withdrawn.

According to the action, claims 13 and 17 are rejected under 35 USC 103(a) as being unpatentable over Aggarwal (WO 9709877) in view of Schneider (US patent 6,013,273). This is respectfully traversed.

As explained above Aggarwal does not disclose or suggest the claimed invention .

As for the view of Schneider et al that use of anti-oxidant teaches septic shock is concerned, that is not true for every anti-oxidant until examined in the body. For example, a well known natural compound, quercetin which has a good anti-oxidant activity (Lee et al, 1982; Lanni and Becker, 1985; Kim et al, 2004), when tested in the animals produced an adverse effect in the body rather than giving any relief (Jones and Hughes, 1982).

Therefore, there is no combination of Aggarwal and Schneider that can make the claimed invention obvious.

It is respectfully requested that the rejection be withdrawn.

Accordingly, it is submitted that the present application is in condition for allowance.

Respectfully submitted,

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